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10/682,130	10/07/2003	Dennis M. Klinman	4239-66902-01	1348

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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
09/10/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/682,130	KLINMAN ET AL.
	Examiner	**Art Unit**
	Nina A. Archie	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 18 June 2010.
2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 35,46,47,54,60-74,76-78 and 80-87 is/are pending in the application.
  4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) 35, 46-47, 54, 60-74, 76-78, and 80-87 is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
  Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
  Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  a)☐ All b)☐ Some * c)☐ None of:
    1.☐ Certified copies of the priority documents have been received.
    2.☐ Certified copies of the priority documents have been received in Application No. _____.
    3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
  * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is responsive to Applicant's amendment and response filed on 6/18/2010 has been entered into the record. Claim 35, 46, 54, and 86-87 are amended. Claims 1-34, 36-45, 48-53, 55-59, 75, and 79 are cancelled. Claims 35, 46-47, 54, 60-74, 76-78, and 80-87 are pending and under examination.

2. The declaration under 37 CFR 1.132 filed 6/18/2010 by Ihsan Gursel, Ph.D. is considered.

Objections/Rejections Withdrawn

3. In view of the Applicant's amendment and remark following objections are withdrawn.

a) Rejection of claims 35, 54, 60-77, and 87 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in light of applicant's amendment, applicant's arguments, and applicant's declaration.

Claim Rejections Maintained-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The rejection of claims 35, 46-47, 54, and 60-87 under 35 U.S.C. 112, first paragraph (scope of enablement) is maintained for the reasons set forth in the previous office action.

The specification is enabled for a method of reducing the production of TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject a suppressive oligodeoxynucleotide (i.e. oligonucleotide), wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof.

Additionally the specification is enabled for a method of reducing the production TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell *in vitro*, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof.

However the specification does not reasonably provide enablement for a method of reducing the production of a cytokine or chemokine in a subject, wherein the cytokine or chemokine is tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocyte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof (clam 35). Moreover, the specification does not provide enablement for a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocyte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as SEQ ID NO: 1, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length (claim 46); a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocyte-derived chemokine (KC) in a cell *in vitro*, comprising contacting the cell specifically with a suppressive oligodeoxynucleotide, wherein the suppressive oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, or a combination of two or more thereof (claim 54). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph (scope of enablement), June 18, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant arguments:

(A) Applicants argue the claims are narrow in scope and the amended claims are limited to methods of reducing four cytokines (TNF, MIP-2, IL-6 and KC) using suppressive ODNs that comprise the Sequences of SEQ ID NO: 1 (claim 35), SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, or a combination of two or more thereof (claim 46 and 54). Applicants argue these ODNs are at most 30 nucleotides in length, and have two to four guanonsine rich sequences and form a G- tetrad. Claims 60, 70-74 and 78 are limited to methods for reducing the expression of TNF, MIP-2, IL-6 and KC wherein the ODN consists of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 21. Applicants argue the methods are limited to reducing ODNs have a specified sequence, length and physical characteristics.

(B) Applicant argue the state of the prior art. Applicants argue the U.S. Patent and Trademark Office (PTO) has previously acknowledged that synthesis of ODNs, administration of ODNs to a subject of interest, and art- recognized models for testing therapies are well known in the art (see the Office action dated May 16, 2008). Applicants argue the methods for measuring TNF, MIP-2, IL-6, and KC is well known in the art; kits to measure these cytokines are commercially available. Applicants argue the US PTO has previously acknowledged that the level of ordinary skill in the art is of a molecular biologist and/or pulmonologist is high (see the Office action dated May 16, 2008). Applicants assert that given the disclosed ODN sequences, one of skill in the art could readily make and use the claimed invention.

(C) Applicants argue the level of predictability in the art. Applicants argue the production of ODNs comprising the sequences set a specified nucleic acid sequence and of a specified length is routine in the art. Applicants argue there are methods, such as ELISAs (or ELISPOT) that are commercially available that can be used to measure cytokine production. Applicants argue the Office has acknowledged that there are art recognized models for inflammatory lung disease that can be used to test the effects of the ODNs of interest in vivo. Applicants argue exemplary results documenting the reduction in cytokine expression are also provided in the specification (see, for example, pages 34-35).

(D) Applicants argue the specification provides the sequences of the ODNs for use in the claimed methods (for example, Table 1, page 22). Applicants argue the specification further provides pharmaceutical compositions and methods of administration of ODNs (for example, page 24, line 9 to page 30, line 10) and methods for determining the effectiveness of an ODN, including methods for measuring cytokine or chemokine production (for example, page 30, line 11 to page 31, line 26; page 32, line 25 to page 34, line 16). Applicants argue the specification provides the sequences of ODNs for use in the claimed methods and provides the use of an exemplary ODN (SEQ ID NO: 1) in inhibiting cytokine production in vitro (Example 2) and in an animal model of inflammation (Example 3). Applicants have provided substantial evidence documenting showing that other ODNs from the group of sequences of SEQ ID NOs: 2-25 have subsequently been shown to be useful in reducing the production of cytokines, for example, Yamada et al. (J. Immunol. 169:5590-5594, 2002; of record) shows that suppressive ODNs H 154 and 1502 (Table 1, SEQ ID NOs: 1 and 20, respectively) inhibit production of Il-6, IL-12 and interferon-gamma (see e.g. Figures 1, 2 and 4, page 5591). Applicants state Shirota et al. (J. Immunol. 174:4579-4583, 2005; submitted previously) teach that suppressive ODN A151 (SEQ ID NO: 2) inhibits IFN-gamma, production in BLAB/c mice treated with LPS (see e.g., Figure 5A, page 4581).

(E) Applicants argue the limited experimentation and the predictable results are also demonstrated in the Declaration of Dr. Gursel. Applicants argue Gursel et al. (J. Immunol. 171:1393-1400, 2003; submitted previously) show that ODNs having the sequences of SEQ ID NOs: 1, 2, 3, 4, 7, and 12 suppress cytokine production in BALB/c spleen cells (see e.g., Figure 3A (SEQ ID NOs: 2, 3, 4, and 7) and Figure 3D (SEQ ID NOs: 1 and 12), page 1396). Applicants argue in vivo administration of the suppressive ODN of SEQ ID NO: 2 inhibited cytokine production in mice (Gursel et al. Figure 5, page 1398). Applicants argue ODNs disclosed in the specification were shown to inhibit cytokine expression induced by either CpG or LPS. Applicants argue the Declaration of Dr. Gursel describes results achieved using the ODNs and the methods disclosed in the specification. Dr. Gursel tested the effect of ODNs comprising SEQ ID NO: 14, 17, 18, 19 and 21 to suppress cytokine production. ODNs comprising the nucleic acid sequence set forth as SEQ ID NO: 14, 17, 18, 19 and 21 reduced expression of TNF, IL-6, MIP-la and MIP-3a. Applicants argue Dr. Gursel did not specifically examine the production of MIP-2 or KC, the Declaration provides a scientific explanation and citations that support the assertion that one of skill in the art would also accept that the production of these cytokines should also be reduced. Applicants argue the Declaration provides evidence that the specification is fully enabling for the claimed methods. In fact, nucleic acid molecules including SEQ ID NO: 1, 14, 17, 18, 19 and 21 have been tested and demonstrated to reduce cytokine expression, using exactly the methods described in the specification.

Examiner's Response to Applicant's Arguments:

With regard to Point (A), the specification discloses a suppressive oligodeoxynucleotide (ODN) H154 (SEQ ID NO: 1), CpG ODN 1555 (SEQ ID NO: 27), and a neutral ODN 1612 in Examples (see Example 1 (see pp. 32-33). The specification discloses CpG DNA stimulates RAW 264.7 cells to produce a variety of cytokines and chemokines (TNFα, MIP-2, IL-6, and keratinocyte-derived cytokine [KC]) (see Example 2 (see pp. 34-35)). The specification discloses the suppressive ODN to CpG-stimulated RAW 246.7 cells significantly reducing production of the pro-inflammatory molecules (see Figure 2 and pg. 35 Example 2). The specification discloses when suppressive ODN were co-administered with the CpG DNA, the suppressive ODN blocks the CpG DNA-induced inflammation of the mouse lung by reducing the production (TNFα, MIP-2, IL-6, and KC), wherein, the CpG DNA triggered the production of pro-inflammatory cytokines and chemokines (TNFα and MIP-2) (see Example 3 (see pp. 35-36 and Figs. 3 and 4). Therefore the specification is limited to a method of reducing the production of TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject, a suppressive oligodeoxynucleotide (i.e. oligonucleotide), wherein the oligodeoxynucleotide is SEQ ID NO: 1. The specification is also limited to a method of reducing the production TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell *in vitro*, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NO: 1. The examples and data set forth in the specification do not enable the instantly claimed invention because there is no evidence of a method of reducing the production of TNFα, MIP-2, IL-6, and KC administering only a suppressive oligonucleotide *in vivo* or *in vitro*. Therefore the specification is not representative of the instant claims. Therefore although the claims have been amended and narrow in scope, the specification is not representative of the claims.

With regard to Point (B), Examiner agrees the synthesis of ODNs, administration of ODNs to a subject of interest is used in art-recognized models for testing therapies are well known in the art. Examiner agrees with the methods for measuring TNF, MIP-2, IL-6, and KC are well known in the art and kits to measure these cytokines are commercially available. Examiner agrees the level of ordinary skill in the art is of a molecular biologist and/or pulmonologist is high. Examiner agrees that with the disclosed ODN sequences that one of skill in the art could readily make and use the claimed invention; however the specification is not representative of the instant claims. Consequently, the examples and data set forth in the specification does not enable the instantly claimed invention because there is no evidence of a method of reducing the production of TNFα, MIP-2, IL-6, and KC administering only a suppressive oligonucleotide *in vivo* or *in vitro*.

With regards to Points (C), (D), and (E), Examiner agrees the art recognized models for inflammatory lung disease that can be used to test the effects of the ODNs of interest in vivo however the claims are not limited to the instant invention. Examiner agrees the production of ODNs comprising the sequences set a specified nucleic acid sequence and of a specified length is routine in the art. Examiner agrees there are methods, such as ELISAs (or ELISPOT) that are commercially available that can be used to measure cytokine production. However, the claims are drawn to a method of reducing the production of TNFα, MIP-2, IL-6, and KC comprising administering a suppressive oligodeoxynucleotide of SEQ ID NOs: 1, 14, 17, 18, 19 and 21 or a combination thereof and a method of reducing the production TNFα, MIP-2, IL-6, and KC in a cell *in vitro*, comprising contacting the cell with suppressive oligodeoxynucleotide of SEQ ID NOs: 1, 14, 17, 18, 19 and 21 or a combination thereof. Moreover, the specification discloses a suppressive oligodeoxynucleotide (ODN) H154 (SEQ ID NO: 1), CpG ODN 1555 (SEQ ID NO: 27), and a neutral ODN 1612 in Examples (see Example 1 (see pp. 32-33)). The specification discloses CpG DNA stimulates RAW 264.7 cells to produce a variety of cytokines and chemokines (TNFα, MIP-2, IL-6, and keratinocyte-derived cytokine [KC]) (see Example 2 (see pp. 34-35)). The specification discloses the suppressive ODN to CpG-stimulated RAW 246.7 cells significantly reducing production of the pro-inflammatory molecules (see Figure 2 and pg. 35 Example 2). The specification discloses when suppressive ODN were co-administered with the CpG DNA, the suppressive ODN blocks the CpG DNA-induced inflammation of the mouse lung by reducing the production (TNFα, MIP-2, IL-6, and KC), wherein, the CpG DNA triggered the production of pro-inflammatory cytokines and chemokines (TNFα and MIP-2) (see Example 3 (see pp. 35-36 and Figs. 3 and 4). Consequently, the specification is limited to a method of reducing the production of TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject, a suppressive oligodeoxynucleotide (i.e. oligonucleotide), wherein the oligodeoxynucleotide is SEQ ID NO: 1. The specification is also limited to a method of reducing the production TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell *in vitro*, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NO: 1. Hence one skilled in the art would accept the *in vivo* efficacy to correlate to the *in vitro* data.

Moreover the declaration discloses results documenting the reduction in cytokine expression of TNFα, MIP-2, IL-6, and KC *in vitro* by contacting a cell with an immuostimulatory CpG and a suppressive oligodeoxynucleotide selected from the group consisting of SEQ ID NOs: 14, 17, 18, 19 and 21 (see pgs. 2-3 of declaration filed 6/18/2010). Therefore the declaration is limited to a method of reducing the production TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell *in vitro*, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with suppressive oligodeoxynucleotide (i.e. oligonucleotide), wherein the oligodeoxynucleotide is SEQ ID NO: 1. Therefore the declaration is also limited to a method of reducing the production of TNFα, MIP-

2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject, suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is one or more SEQ ID NOs: 14, 17, 18, 19 and 21 because one skilled in the art would accept the *in vitro* data to correlate with *in vivo* efficacy. Consequently, the declaration under 37 CFR 1.132 filed 6/18/2010 signed by Ihsan Gursel, Ph.D. is insufficient to overcome the rejection because the evidence in the declaration is not in commensurate in scope with the instant claims which are not limited to any induction of an immunostimulatory CpG, thus the Declaration is deemed unpersuasive. Even though the declaration provides a scientific explanation and citations that support the assertion that one of skill in the art would also accept that the production of these cytokines should also be reduced the declaration is unpersuasive because the evidence in the declaration is not commensurate in scope with the instant claims. The declaration is enabling for the specification but the declaration does not enable for the instant claims. Consequently, the examples and data set forth in the declaration and in the specification does not enable the instantly claimed invention because there is no evidence of a method of reducing the production of TNFα, MIP-2, IL-6, and KC administering only a suppressive oligonucleotide *in vivo* or *in vitro*.

As outlined previously, the specification is enabled for a method of reducing the production of TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject a suppressive oligodeoxynucleotide (i.e. oligonucleotide), wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof.

Additionally the specification is enabled for a method of reducing the production TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell *in vitro*, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof.

However the specification does not reasonably provide enablement for a method of reducing the production of a cytokine or chemokine in a subject, wherein the cytokine or chemokine is tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocvte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof (clam 35).

Moreover, the specification does not provide enablement for a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocvte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as SEQ ID NO: 1, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length (claim 46); a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocvte-derived chemokine (KC) in a cell *in vitro*, comprising contacting the cell specifically with a suppressive oligodeoxynucleotide, wherein the suppressive oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, or a combination of two or more thereof (claim 54). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;
(B)The nature of the invention;
(C)The state of the prior art;
(D)The level of one of ordinary skill;
(E)The level of predictability in the art;
(F)The amount of direction provided by the inventor;
(G)The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The claims are drawn to a method of reducing the production of a cytokine or chemokine in a subject, wherein the cytokine or chemokine is tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocvte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises from 2 to 4 guanosine-rich sequences and forms a G-tetrad, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length or a combination of two or more thereof (clam 35); a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocvte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as SEQ ID NO: 1, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length (claim 46); a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocvte-derived chemokine (KC) in a cell *in vitro*, comprising contacting the cell specifically with a suppressive oligodeoxynucleotide, wherein the suppressive oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, or a combination of two or more thereof (claim 54).

Breadth of the claims: The claims encompasses suppressive oligodeoxynucleotides (SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) or a combination of two or more suppressive oligodeoxynucleotides thereof (SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) in a method of reducing the production of TNFα, MIP-2, IL-6, and KC administering solely one or more suppressive oligonucleotide *in vivo* or *in vitro* without the administration of an immunostimulatory CpG with one or more said suppressive oligodeoxynucleotides is overly broad. Therefore it is hard for one skilled in the art to determine if the suppressive oligodeoxynucleotides (SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) or a combination of two or more can be used for in the recited methods as claimed. Furthermore it is hard for one skilled in the art to determine if the performance of the recited methods correlate to the outcome of a method of reducing the production of a (TNF), (MIP)-2, (IL)-6 or (KC) in a subject *in vivo* or in a cell *in vitro* because there is no evidence of a method of reducing the production of TNFα, MIP-2, IL-6, and KC administering only a suppressive oligonucleotide *in vivo* or *in vitro*.

Guidance of the specification/The existence of working examples:

The specification discloses a suppressive oligodeoxynucleotide (ODN) H154 (SEQ ID NO: 1), CpG ODN 1555 (SEQ ID NO: 27), and a neutral ODN 1612 in Examples (see Example 1 (see pp. 32-33). The specification discloses CpG DNA stimulates RAW 264.7 cells to produce a variety of cytokines and chemokines (TNFα, MIP-2, IL-6, and KC) (see Example 2 (see pp. 34-35)). The specification discloses the suppressive ODN to CpG-stimulated RAW 246.7 cells significantly reducing production of the pro-inflammatory molecules (see Figure 2 and pg. 35 Example 2). The specification discloses when suppressive ODN were co-administered with the CpG DNA, the suppressive ODN blocks the CpG DNA-induced inflammation of the mouse lung by reducing the production (TNFα, MIP-2, IL-6, and KC), wherein, the CpG DNA triggered the production of pro-inflammatory cytokines and chemokines (TNFα and MIP-2) (see Example 3 (see pp. 35-36 and Figs. 3 and 4).

Consequently, the specification is limited to a method of reducing the production of TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject, suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NO: 1. The specification is also limited to a method of reducing the production TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell *in vitro*, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NO: 1. Hence one skilled in the art would accept the *in vivo* efficacy to correlate to the *in vitro* data. However, the examples and data set forth in the specification does not enable the instantly claimed invention because there is no evidence of a method of reducing the production of TNFα, MIP-2, IL-6, and KC administering only a suppressive oligonucleotide *in vivo* or *in vitro*. Therefore the specification is not representative of the instant claims and the specification is not fully enabled for the instant claims.

In conclusion, the claimed invention does not provide enablement for a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocvte-derived chemokine (KC), comprising administering specifically to the subject a suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide comprises the nucleic acid sequence set forth as SEQ ID NO: 1, wherein the oligodeoxynucleotide is 10 to 30 nucleotides in length (claim 46); a method of reducing the production of tumor necrosis factor (TNF), macrophage inflammatory protein (MIP)-2, interleukin (IL)-6 or keratinocvte-derived chemokine (KC) in a cell *in vitro*, comprising contacting the cell specifically with a suppressive oligodeoxynucleotide, wherein the suppressive oligodeoxynucleotide comprises the nucleic acid sequence set forth as one of SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, or a combination of two or more thereof (claim 54). The claims encompass the suppressive oligodeoxynucleotides (SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) or a combination of two or more suppressive oligodeoxynucleotides thereof (SEQ ID NO: 1, SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21) in a method of reducing the production of TNFα, MIP-2, IL-6, and KC administering only one or more suppressive oligonucleotide *in vivo* or *in vitro* solely without the administration of an immunostimulatory CpG with one or more said suppressive oligodeoxynucleotides is overly broad. Therefore it is hard for one skilled in the art to determine if the performance of the recited methods correlate to the outcome of a method of reducing the production of a (TNF), (MIP)-2, (IL)-6 or (KC) in a subject *in vivo* or in a cell *in vitro* because there is no evidence of a method of reducing the production of TNFα, MIP-2, IL-6, and KC administering only a suppressive oligonucleotide *in vivo* or *in vitro*. Consequently, the specification is limited to a method of reducing the production of TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG comprising the steps of a) administering said immunostimulatory CpG to a subject and b) administering to the subject, suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NO: 1. The specification is also limited to a method of reducing the production TNFα, MIP-2, IL-6, and KC induced by an immunostimulatory CpG in a cell *in vitro*, comprising the steps: a) contacting the cell with said immunostimulatory CpG and b) contacting the cell with suppressive oligodeoxynucleotide, wherein the oligodeoxynucleotide is SEQ ID NO: 1. However, the examples and data set forth in the specification does not enable the instantly claimed invention because there is no evidence of a method of reducing the production of TNFα, MIP-2, IL-6, and KC administering only a suppressive oligonucleotide *in vivo* or *in vitro*. Therefore the specification is not representative of the instant claims and the specification is not fully enabled for the instant claims. Moreover, since the specification and declaration filed on 6/18/2010 is not representative of the instant claims, the claimed methods are not enabled.

New Objections

Specification and Declaration

5. The disclosure is objected to because of the following informalities: the specification and declaration recites "RAW 246.7 cells" (see pg. 2 of declaration and example 2 of the specification), however the specification also states "RAW 264.7 cells" (see example) which appears to be a typographical error. Clarification is required for the RAW cells aforementioned above. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. Appropriate correction is advised.

Conclusion

6. No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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